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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,350	SCHINDLER ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/497,723.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The claims in this application are the claims 1-10 related to compounds, composition, and method of making and method of use of Formula I.

Specification

The disclosure is objected to because of the following informalities: The specification should be amended as:" This application is a Div of U. S. Application Sr. No. 09497723 filed 2/4/2000, now U.S.P. 6660746 which claims priority of De 19904710.3 filed 2/5/1999.

Appropriate correction is required.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/1/03 is being considered by the examiner. Signed copy of the PTO Form 1449 is enclosed with this communication for applicants' record.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-3,6,7,8,10. are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-3,6,7,8,10,11,12, 13 of U.S. Patent No. 6660746. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims overlap the patented invention.

3. The ref. '746 claims 1-3,6,7,8,10,11,12, 13 recite the compounds of Formula I, their composition, a method of making, and specific method of use. See claim 1-3 for compounds, columns 20-21. Ref. '746 recites claim 6 as a method of making the compounds in column 22 lines 5-27, claim 7 as a pharmaceutical composition of compounds of claim 1 in column 22 lines 28-30.

4. Instant claim 10 differ from the ref. '746 claims by reciting a broader scope but they also read onto the ref.'746 claims, which would extent, the monopoly of the U.S.P.6660746.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

5. Claims 1 recite R1 and R2 components as:" C3-C7 cycloalkyl ... or are C3-C9 cycloalkyl which ca be substituted ...". It is not very clear as to what applicants want to present with. Are the compounds of C8-C9 unsubstituted in nature excluded to avoid any prior art(s)? Correction is required.

6. Claim 2 which is dependent on claim s recites:" ... and the other of the residues R1 and R2 is.... C3-C7-cycloalkyl...or is C3-C9-cycloalkyl optionally substituted by one

or more...". The claim as presented reads onto a wider scope rather limiting the scope. Correction is required.

7. Claim 1 in lines 25-27 on page 37 recites:" aryl is phenyl, naphthyl, or heteroaryl". Does aryl include heteroaryl rings? Correction is required. In re Sus et al., 135 USPQ 301 ; In re Lund et al., 153 USPQ 625.

8. Claims 1-4 recite:" variables as:" optionally substituted by one or more identical or different subtituents". The claims remain silent about the exact and definite number of substituents and the exact position occupied by the same in a ring or chain (where applicable). Correction is required.

9. Claim 9 recites:" A method for activating at least one soluble guanylate cyclase, comprising adding at least one compound of Formula I as claimed in claim 1 to said at least one soluble guanylate cyclase". The use of " at least one" is not acceptable. Petrolite Corp, v, Watson, Comm. Pats., 113 USPQ 248.

10. Claim 10 recites the words : " at least one". For reason(s) see 9. above.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim9, 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a single and definite disorder (e.g. hypertension), does not reasonably provide enablement for ***treating or preventing***

disorders associated with a method for activating at least one soluble guanylate cyclase, comprising adding at least one compound of Formula I as claimed in claim1 to said at least one soluble guanylate cyclase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims are not limited to a single and definite disorder but also include include strike, thrombosis, erectile dysfunction, bronchial asthma, diabetes, improving restricted learning capacity or memory power and disorders yet to be discover as recited herein.

13. In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

14. " Compounds and their Pharmaceutical compositions of at least one compound of Formula I and a physiologically acceptable carrier as recited herein read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its composition with other physiologically acceptable carrier". Applicants provide no reasonable assurance those any and all compositions of

the instant compounds and their combinations either alone (or in a combination as recited in claim 9) as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

15. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn in part to treating or preventing of diseases caused by cGMP. The diseases include in addition to hypertension, erectile dysfunctions, diabetes, stroke, improving restricted learning capacity or memory power, and many others as recited herein.
2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat or prevent restricted learning capacity or memory power nor is there any compound that can be used to treat erectile dysfunctions, diabetes, and other diseases by a single compound. For example, the notion that a compound could be effective against diseases related to different body organs of male sexual organ as well as female memory power. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites".
3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which are responsive to the activity of cGMP receptors. There is no evidence of record which would enable the skilled artisan in the identification of the diseases and curative or prophylactic treatment(s) of the disorders claimed herein.
4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses or patient dosage regim present for treatment or prevention of the disorders recited.
6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following references are cited to show the state of art related to a few of the diseases recited herein:

Following references are cited to show the present state of art(s) for AD: Understanding about Alzheimer's disease:

- Cecil's Textbook of Medicine, vol2, 20th Edn. (see pages1992-1996) for AD related Dementia, and in particularly Table 400-1 listing The most frequent causes of progressive dementia in page 1992.

- Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

- **References to cite the state of art(s) related to cGMP:**

  - **Mechanism and effects by competition products(=BAY 41-2272):**

Bischoff et al(PubMed Abstract 12597982, also cited as Urology, 61/2,464-7(2003)) state that:" The time-course and onset of erection was concurrent with stimulation by exogenous NO(SNP), suggesting that this new pharmacological mechanism of soluble guanylyl cyclase stimulation could be used in the treatment of erectile dysfunction. Because the effect is increased by SNP, it can be expected that BAY 41-2272 would have enhanced activity during sexual arousal, when NO is produced endogenously".

  - **Effect of known drug, Sildenafil on cerebral blood flow velocity:**

Arnavaz et al(PubMed Abstract 12694895, also cited as Psychiatry Res. 122/3, 207-9(2003)) state that:"Neither the intake of Sildenafil nor application placebo resulted in any significant changes in blood flow velocity of the right middle cerebral artery. The next step for future experiments will be in vitro measurement of the diameters of the cerebral arteries under the influence of Sildenafil and in vivo measurement of CO2 and cerebral blood flow velocity during sexual stimulation after Sildenafil intake instead of under restir conditions".

  - **Efficacy and safety of known drug: Sildenafil citrate in treatment of erectile dysfunction in patients with ischemic heart disease:**

Conti et al(PubMed Abstract 10078540, also cited as Am. J. Cardiol. 83/5A, 29C-34C(1999)) state that:" Physicians should be aware that patients with under lying

cardiovascular disease could be adversely affected by the vasodilator effects of Sildenafil, especially in combination with sexual activity".

16. Specification on pages 33-35 recite various Pharmacological Investigations, methods of assays and tests carried out for instant compounds, and applicants summarize the results in Table 2 in page 35 for 14 selected compounds as n-fold stimulation (at c = 50uM).

The results show that these compounds have a range from 14 – 28 n-fold stimulation at concentration c = 50 uM , and exibit activity as inhibitors of cGMP at 50uM".

These results are not sufficient to support the methods of use claims claiming not only treating, but also preventing restricted learning capacity or memory power nor is there any compound that can be used to treat erectile dysfunctions, diabetes, and other diseases by a single compound as recited herein. These results will help as a preliminary guideline for screening the compounds only.

17. Statements of utility, which relate to or imply to treatment of a disease/disorder are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claim 16 does not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

18. The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

Allowable Subject Matter

19. The following is a statement of reasons for the indication of allowable subject matter: Compound Claim 5, process claim 7 related to claims 5 compounds, composition claim 8 related to compounds of claim 5 would be considered for allowance if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and other ejections, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Method of use claim 10 related to claim 5 compounds for treating a single and specific disorder would also be considered for allowance provided applicants submit required evidence as stated earlier.

The closest prior art ref. Chen (U.S.P. 4306065) teaches making of compounds with a core: " 4-piperidinol or 3-pyrrolidinol, 1-(2-phenyl-4-quinazolinyl)-" wherein the quinazoline is unsaturated and phenyl is unsubstituted as well.

The reference does not indicate or suggest to arrive at the instant compounds wherein phenyl is substituted.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sudhaker B. Patel, D.Sc. Tech.
April 5, 2004

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ART UNIT 1624/1623